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Non-rigid Multimodal Medical Image Registration Based on the Conditional Statistics of the Joint Intensity Distribution

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Abstract

In this paper, we present a new methodology for multimodal non-rigid medical image registration. The proposed approach is based on combining a rigid registration achieved by a global optimization method, and a multimodal optical flow technique based on the conditional statistics of the joint intensity distribution (CS-JID) of the images to register. The methodology is essentially composed of two steps: first, the global deformation is approximated by using a rigid registration based on particle filtering; second, the optical flow is applied iteratively between the target and sequentially registered source image, by optimizing a new energy function that penalizes the difference between the intensities in one image with respect to the mean of the conditional intensity distribution of the other image, weighted by the conditional variance. After these steps, the non-rigid registration is made up by adding the resulting vector fields, computed by the rigid registration, and the sequential optical flow. The proposed algorithm was tested with three pairs of computed tomography (CT) and magnetic resonance (MR) images, aligned in the acquisition process, and subsequently warped with a synthetic non-rigid deformation. Preliminary results show that the methodology presents a good alternative for non-rigid multimodal registration, obtaining an average error of less than one pixel in the estimation of the deformation vector field in the majority of the cases.

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Keywords: Non-rigid registration, multimodal images, medical imaging, optical flow

1. Introduction

Image registration is an important task in digital image processing and medical imaging [1, 2], since it can be used in several important processes like: characterization of the heart anatomical changes in a cardiac cycle or gradual atrophy of the brain in ageing, modeling of anatomic structures, tissues segmentation

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through medical atlases, correction of artefacts caused by movement in fetal images, among many others [2, 3, 4]. According to the types of deformations that one wishes to achieve, image registration can be divided in two main streams: rigid or parametric registration, and elastic or non-rigid.

In the literature, the rigid problem has been studied extensively [2], where the registration algorithm is formulated basically as a minimization process of a cost function that depends on a small set of parameters of a geometric transformation (affine or perspective [5]). The goal of these methods is to obtain a set of parameters describing the geometric mapping between the target and source images by optimizing a similarity metric (e.g. Mutual Information) [3], by using for this purpose algorithms like gradient descent [6], or more recent approaches based on global optimization techniques such as genetic algorithms [7], or particle filtering (PF) [8, 9].

On the other hand, the non-rigid registration (NRR) is a more complex and involved problem, especially for multimodal images; however it has a greater number of applications in medical imaging [4]. In the literature, the most common method to solve the elastic registration is through splines, where a family of functions are used to approximate the complex deformations by seeking their best parameters through optimizing a similarity metric, but the main drawback of these methods is their complexity and their high computational cost [10, 11, 12]. A most recent proposal to solve the NRR problem is based on an iterative optical flow (OF) [13] framework in order to find the deformation vector field, after conducting an initial rigid registration using the PF [14]; this method has shown promising results in [15] and [16]. Nonetheless, an important restriction of this algorithm is the hypothesis of intensity conservation between images, restricting the solution to unimodal images or the necessity of an injective intensity transfer function between the target and source images, which is difficult to construct in the case of multimodal medical image registration. In this context, [17] proposed to map the images into a common domain, using local variability measures (LVM), where their intensities can be compared, and next to apply an iterative OF using scale space [18], in order to overcome the unimodal restriction in [14]. In fact, the main problem of this technique is their dependence on textures and contrast with the background in the images. Thus, in this work, we propose a new methodology where the problem of multimodal NRR could be solved by applying an iterative OF by minimizing a new energy function that penalizes the difference between the intensities in an image with respect to the mean value of the conditional intensity distribution of the other image, weighted by their conditional variance; where this procedure is applied after an initial estimation of the displacements vector field by a rigid registration using the PF.

The paper is organized as follows: in section 1 we introduce and explain the basic ideas of the proposed methodology; in subsections 2.1 and 2.2, the rigid registration based on PF, and the non-rigid version based jointly on OF and PF is reviewed, respectively, and the new methodology is described in subsection 2.3; the evaluation of the proposal is carried out by using real data with synthetic deformations in subsection 2.4. In sections 3 and 4, we describe the experimental results and their discussion. Finally, in section 5, some conclusions are drawn about this work, and also future research lines are discussed.

2. Methodology

NRR can be formulated as finding the displacements vector field $V(\mathbf{r})$ such that it can align a source image I_S with a target one I_T. NRR can be mathematically written as follows:

$$I_T(\mathbf{r}) = F\left[I_S(\mathbf{r} + V(\mathbf{r}))\right], \tag{1}$$

where $\mathbf{r}$ is the coordinates vector of the pixel or voxel, and $F[\cdot]$ represents the relation between the intensities of both images. According to (1), if the two images are unimodal, the mapping F is the identity and the registration problem can be seen as to find the OF such that both images are aligned. However, OF techniques can find only small displacements between the correspondent pixels. In this way, it is convenient to have an initial estimation of the deformation vector field $V(\mathbf{r})$ by using a rigid registration, for example based on the PF [8].

2.1. Rigid registration based on PF

The basic idea of the rigid registration based on PF is to estimate a parameters vector of a geometrical transformation (e.g. affine) by an stochastic search over an optimization surface. This goal is achieved by using a set of N test points called particles $(\boldsymbol{\theta}_1, \ldots, \boldsymbol{\theta}_N)$, and their associated weights $(W_1, \ldots, W_N)$ calculated by a *likelihood* function $P(z|\boldsymbol{\theta}_j)$ for a measurement z between the images,

$$W_j = \frac{1}{\sqrt{2\pi}\sigma_\eta} \exp\left\{-\frac{\left(2 - \mathrm{NMI}\left\{I_T(\mathbf{r}), I_S(T(\mathbf{r}|\boldsymbol{\theta}_j))\right\}\right)^2}{2\sigma_\eta^2}\right\} \quad j = 1, \ldots, N, \tag{2}$$

where $T(\mathbf{r}|\boldsymbol{\theta})$ is a geometrical transformation depending on the parameters vector $\boldsymbol{\theta}$, σ_η^2 is the noise variance in the measure, and $\mathrm{NMI}(\cdot, \cdot)$ represents the normalized mutual information [19] between two images; the NMI metric offers a better performance for rigid registration based on PF, as it is reported in [20]. The weights W_j are used to approximate the a posteriori probability density function $P(\boldsymbol{\theta}|z)$ of the unknown parameters $\boldsymbol{\theta}$ given a measurement z. In this way, for a window of k observations $(z^1, \ldots, z^k)$, the estimated vector $\hat{\boldsymbol{\theta}}^k$ of the rigid transformation can be computed by the expected value of the approximated probability density function, i.e. $\hat{\boldsymbol{\theta}}^k = E[\boldsymbol{\theta}|z^1, \ldots, z^k]$ [21]. As a consequence, the resulting rigid transformation of the coordinates vector $\mathbf{r}$ can be defined a $d_0(\mathbf{r}) = T(\mathbf{r}|\hat{\boldsymbol{\theta}}) - \mathbf{r}$. For more details of the implementations of this technique, the reader is referred to [8, 9, 15, 20].

2.2. Unimodal non-rigid registration based on PF and OF

Once achieved the initial rigid registration by using the PF, the displacements of the pixels between the target I_T and source I_S images are expected to be small, and if the images are unimodal, it is possible to find these displacements by using an OF technique. One algorithm that can be used, which is reported in [17] and originally proposed by Horn and Schunck [13], seeks to minimize the following energy function (continuous domain):

$$\varepsilon^2 = \int\int (\varepsilon_b^2 + \alpha\varepsilon_c^2) dx dy, \tag{3}$$

where ε_b is the error in the intensity changes between the target I_T and source I_S images, ε_c is the smoothness measurement of the displacement flow, α is a regularization term to control the flow speed, and x and y the cartesian coordinates. Other technique to solve the OF is used in [14], where it is minimized the following energy function (discrete domain):

$$\psi(d) = \sum_{\forall \mathbf{r}} [I_T(\mathbf{r}) - I_S(\mathbf{r} + d(\mathbf{r}))]^2 + \lambda \sum_{<\mathbf{r},\mathbf{s}>} \|d(\mathbf{r}) - d(\mathbf{s})\|_2^2, \tag{4}$$

where d is the displacements field, $< \mathbf{r}, \mathbf{s} >$ represents the nearest neighbours of $\mathbf{r}$, λ is a regularization term to control flow homogeneity, and $\|\cdot\|$ represents the Euclidean norm.

The quadratic cost functions in (3) and (4) have a similar structure, since both include data error and regularization terms, where their optimal solutions can be computed by solving a linear system of equations for each pixel. For this purpose, efficient iterative methods could be applied, for example the Gauss-Seidel technique. For more implementation details of these techniques, the reader is referred to [13, 14, 17, 22].

Now according to [14], after an initial estimation of the elastic vector field obtained through parametric registration, a recursive process based on OF is suggested to refine the initial estimation by accumulating the vector field obtained after solving the optimization in (4), until a convergence condition is achieved. In the case of multimodal registration, [14] approximates the intensity transfer function between images I_T and I_S using a joint histogram, but this approach is feasible only if the mapping of intensities between the images is injective. Recently, in [17], local variability measures (LVM) are used to map the images into a common domain where their intensities can be compared, but the problem with this technique is its high dependence on textures and contrasts with the background in the images. In this context, in the present work, we propose to estimate the OF by optimizing a new energy function that quadratically penalizes the error between the intensities in an image with respect to the mean of the conditional intensity distribution of the other image, weighted by its conditional variance. In addition, similar to (4), a regularization term is added to avoid an ill-posed problem. In this way, the error terms are evaluated in the intensity ranges associated with each independent image, and consequently, the resulting OF problem can deal with multimodal images.

2.3. Proposed for multimodal non-rigid registration

Given two multimodal images to register $I_T(\mathbf{r})$ and $I_S(\mathbf{r})$, similarly to [14], an initial estimation of the deformation vector field $d_0(\mathbf{r})$ is computed by using the PF optimization of subsection 2.1. With this vector field, the source and target images are transformed such that

$$\tilde{I}_T(\mathbf{r}) = I_T(\mathbf{r} - d_0(\mathbf{r})), \quad \tilde{I}_S(\mathbf{r}) = I_S(\mathbf{r} + d_0(\mathbf{r})) \quad \forall \mathbf{r}. \tag{5}$$

Next based on the structure of the cost function in (4), the remaining displacements $d(\mathbf{r})$ are calculated by optimizing the quadratic energy function described below by using the conditional statistics of the joint intensity distribution (CS-JID):

$$\Upsilon(d) = \sum_{\forall \mathbf{r}} \left\{ \frac{1}{\sigma_S(\mathbf{r})} \left[\mu_S(\mathbf{r}) - \tilde{I}_S(\mathbf{r} + d(\mathbf{r})) \right]^2 + \frac{1}{\sigma_T(\mathbf{r})} \left[\tilde{I}_T(\mathbf{r} - d(\mathbf{r})) - \mu_T(\mathbf{r}) \right]^2 \right\} + \lambda \sum_{<\mathbf{r},\mathbf{s}>} \|d(\mathbf{r}) - d(\mathbf{s})\|_2^2, \tag{6}$$

where $\sigma_S^2(\mathbf{r}) = E[(\tilde{i}_S - \mu_S(\mathbf{r}))^2 | i_T = I_T(\mathbf{r})]$ and $\sigma_T^2(\mathbf{r}) = E[(\tilde{i}_T - \mu_T(\mathbf{r}))^2 | i_S = I_S(\mathbf{r})]$ are the intensity variances with associated intensity expected values $\mu_S(\mathbf{r}) = E[\tilde{i}_S | i_T = I_T(\mathbf{r})]$ and $\mu_T(\mathbf{r}) = E[\tilde{i}_T | i_S = I_S(\mathbf{r})]$, respect to the joint intensity distributions $p(i_T, \tilde{i}_S)$ and $p(\tilde{i}_T, i_S)$ associated to images pairs $(I_T(\mathbf{r}), \tilde{I}_S(\mathbf{r}))$ and $(\tilde{I}_T(\mathbf{r}), I_S(\mathbf{r}))$, respectively. Consequently in equation (6), the first two terms penalize the differences of the intensity in one image respect to the conditional mean in the other, μ_T and μ_S, and weight these differences by the conditional variances σ_T^2 and σ_S^2. Meanwhile, the third term is a regularization component included in order to smooth the resulting displacements field $d(\mathbf{r})$, and to avoid an ill-posed optimization process. It is important to note that the optimization problem in (6) is non-linear, and to solve it, we first approximate the non-linear terms using a first order Taylor's expansion [6],

$$\tilde{I}_S(\mathbf{r} + d(\mathbf{r})) \approx \tilde{I}_S(\mathbf{r}) + \nabla \tilde{I}_S(\mathbf{r})\, d(\mathbf{r})^T, \tag{7}$$

$$\tilde{I}_T(\mathbf{r} - d(\mathbf{r})) \approx \tilde{I}_T(\mathbf{r}) - \nabla \tilde{I}_T(\mathbf{r})\, d(\mathbf{r})^T, \tag{8}$$

where $\nabla\{\cdot\}$ is the gradient operator, and $(\cdot)^T$ denotes the transpose operation. Once expanded the error terms, the derivative of equation (6) with respect to the displacements $d(\mathbf{r})$ can be computed to derive the stationary conditions of the optimization process. Hence the result is a linear system equations for each pixel that can be solved iteratively by using the Gauss-Seidel method to obtain the optimal $d(\mathbf{r})$.

As a result, the proposed methodology to solve the non-rigid multimodal image registration can be summarized in the next three steps:

1. **Rigid registration**. Compute a rigid registration finding the transformation parameters $\boldsymbol{\theta}$ using the PF, and obtain a first approximation of the displacements vector field $d_0(\mathbf{r})$. Then compute the transformed images $(\tilde{I}_T(\mathbf{r}), \tilde{I}_S(\mathbf{r}))$ according to (5).
2. **Multimodal optical flow**. Find the vector field of the OF in an iterative form $d(\mathbf{r}) = d_1(\mathbf{r}) + d_2(\mathbf{r}) + \ldots$, such that (6) is minimized until a convergence condition is satisfied; where at k-th iteration, the joint intensity distribution $p(\tilde{i}_T^k, \tilde{i}_S^k)$ is computed in order to have the best approximation of the tonal transfer function between the images $\tilde{I}_S^k(\mathbf{r}) = I_S\left(\mathbf{r} + \sum_{i=0}^{k-1} d_i(\mathbf{r})\right)$ and $\tilde{I}_T^k(\mathbf{r}) = I_T\left(\mathbf{r} - \sum_{i=0}^{k-1} d_i(\mathbf{r})\right)$, similarly to an iterative expectation maximization algorithm [23].
3. **Compute the non-rigid registration**. Add the vector fields and calculate the displacements that constitute the elastic transformation, $V(\mathbf{r}) = d_0(\mathbf{r}) + d(\mathbf{r})$; then $I_T(\mathbf{r}) \approx F[I_S(\mathbf{r} + V(\mathbf{r}))]$.

Some details to consider during our implementations: i) the joint intensity distribution $p(\tilde{i}_T, \tilde{i}_S)$ can be computed departing from the joint histogram between the images [5], in our evaluation, we employed a resolution of 256×256 bins; ii) the regularization parameter λ in (6) was assigned to a value of 3,000 by a trial-and-error method; and iii) the nearest neighbours $< \mathbf{r}, \mathbf{s} >$ in (6) are calculated by a clique of size two.

2.4. Experiments

In order to obtain a performance evaluation of the proposed algorithm, CT and MR studies of three patients with cerebral tumour before been treated with macroscopically total resection were used, in which the presence of deformations in the head-and-neck tract caused by tumours in the transaxial plane were evident. These patients underwent pre-operative diagnostic and radiotherapy treatment at the San Raffaele Hospital in Milan, Italy. Three CT and MR 2D images of different sections of the head were selected to study different morphological structures. A slice by slice spatial correspondence between CT and MR images was obtained by using the proper protocol for the CT and MR scans acquisition, and the rigid registration (translation and rotation) software available on the Treatment Plan System (TPS). Each slice was of 512×512 pixels with a voxel size of $0.822 \times 0.822 \times 3.000$ mm^3.

An elastic deformation vector field from Thin Plate Splines [24] was generated using the images described in previous paragraph. The vector field of the non-rigid transformation is obtained and applied to the MR image and used as a Ground Truth (GT). As a result, we have three different registration problems as shown in Fig. 1: in the first column, Figs. 1.(a), 1.(e) and 1.(i) show the CT used as a source image; in the second column Figs. 1.(b), 1.(f) and 1.(j) show the MR image used as a target, aligned during acquisition with CT, and synthetically warped for experiments; in the third column Figs. 1.(c), 1.(g) and 1.(k) show the synthetic elastic deformation applied over the aligned MR image to generate the target; and in the fourth column, Figs. 1.(d), 1.(h) and 1.(l) show the overlapped images in BGR (source image in red channel, and target in green one). Next, it is possible to compute the alignment error by using the Euclidean norm of the vector field estimated for the registration algorithm and the GT. The non-rigid registration has been conducted by using the proposed algorithm for the synthetic problems in Fig. 1. Additionally, we conducted the registration problems in Fig. 1 with the algorithm proposed in [17] by using the entropy as a LVM, in order to compare the obtained results with this new methodology.

3. Results and Discussion

The registration results are shown in Fig. 2, where in the first column, Figs. 2.(a), 2.(e) and 2.(i), it is possible to appreciate the source image warped by the proposed method based on CS-JID, for the three GTs. Then, in the second column, Figs. 2.(b), 2.(f) and 2.(j), the superposed registered images in BGR, warped source image in red channel and target in green channel; and in the third column, Figs. 2.(c), 2.(g) and 2.(k), the superposed images in BGR using the warped source image by the LVM method. In column two and three, it is possible to appreciate the differences in the registration accuracy between the two employed algorithms CS-JID and LVM; for example, it can be observed that CS-JID reduce the halo produced by the contrast of the cerebrospinal fluid, when it is exposed to x-ray. This rearrangement of the cerebrospinal fluid halo, numerically increases the error with respect to the GT but anatomically perhaps have greater advantages, since it has a better edge definition of the gray matter and skull on the CT, and in the superposed images in BGR. Moreover, this halo reduction effect does not appear in the LVM method; on the contrary, it seems that the halo is increased slightly in some regions and overlaps the MRI skull.

In the four column of Fig. 2, it is possible to see the error in the estimation of displacements vector field obtained by the proposed method CS-JID, Figs. 2.(d), 2.(h) and 2.(l). The error was computed by the Euclidean norm for the displacements and plotted on the image to detect the spatial location of the error in each pixel. In these subfigures, some distinctive patterns can be observed which are due to the synthetic vector fields obtained by the Thin Plate Splines. So it is clear abrupt changes, in some directions, where exist the intersections of the deformations modeled by the splines. Nonetheless, regardless of the observed patterns, the cooler colors (close to blue) represent small errors, and warmer colors (closer to red) represent greater errors in the estimations, and according to this, we observe that the higher errors occur in the edges of structures and tissues.

Finally, in Table 1 we present a summary of the numerical errors in the estimation of the deformation vector fields, obtained by the proposed algorithm CS-JID and by the LVM method. In this table, the average error and its standard deviation of each GT is showed. Then, the proposed algorithm obtains, in two of the three cases (GT1 and GT2), an average error of less than one pixel in the estimation of the deformation

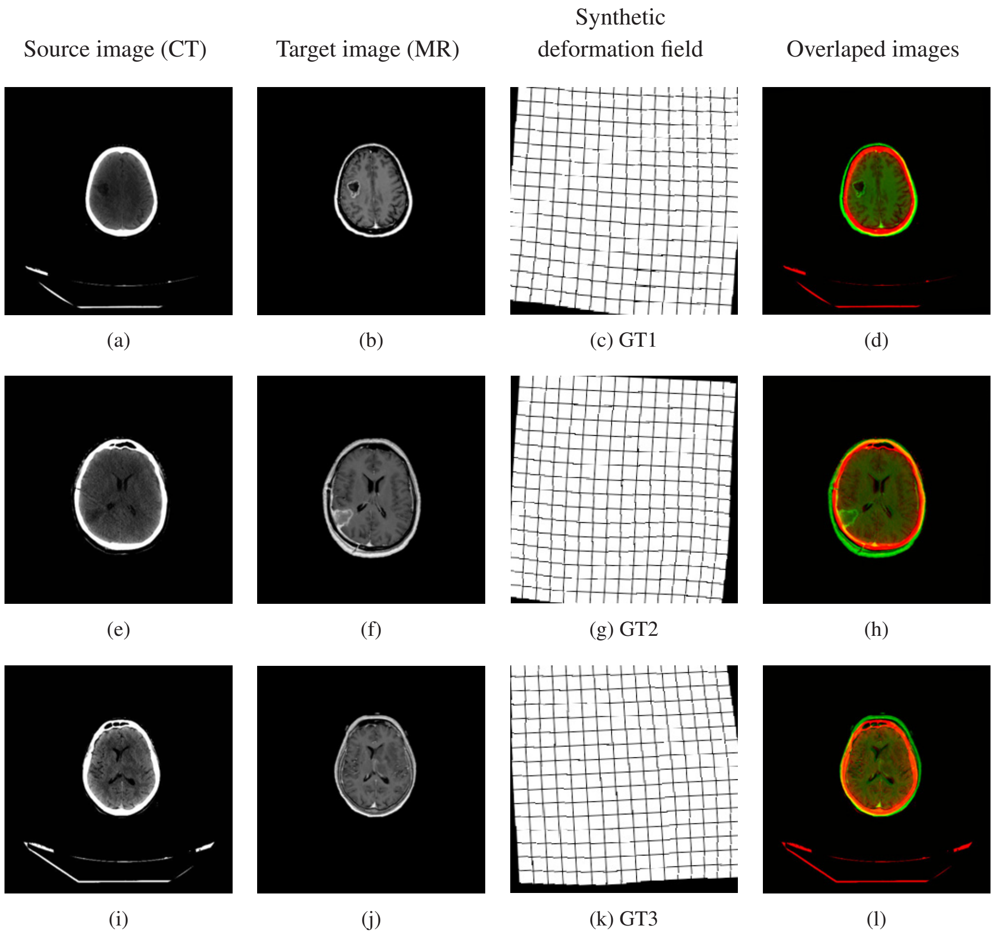

Fig. 1. Non-rigid registration problems employed to evaluate the proposed algorithm. Subfigures (a), (e) and (i) present the CT image used as a source. Subfigures (b), (f) and (j) illustrate the MR image used as a target (aligned during acquisition with CT, and synthetically warped for experiments). Subfigures (c), (g) and (k) show the synthetic deformation applied over the aligned MR image to generate target (GT). Subfigures (d), (h) and (l) present the overlapped images in BGR (source image in red channel and target in green channel).

Table 1. Error in the estimated deformation vector field with respect to the GTs (Euclidean norm) after a non-rigid registration by using the proposed algorithm based on CS-JID, and on LVM [17].

Method	Vector Field Error					
	Average			Std. Dev.		
	GT1	GT2	GT3	GT1	GT2	GT3
CS-JID	0.968	0.524	1.799	0.772	0.366	1.091
LVM	1.679	0.620	1.922	1.076	0.504	1.268

vector field, with a standard deviation less of one pixel too; outperforming, in all three cases, the LVM method, that only had a smaller average error to one pixel in one of the three ground truths (GT2).

4. Conclusions

In this paper, a new multimodal NRR method is proposed which relies on the CD-JID of the target and source images. The algorithm has a two step structure to approximate the non-rigid deformation vector

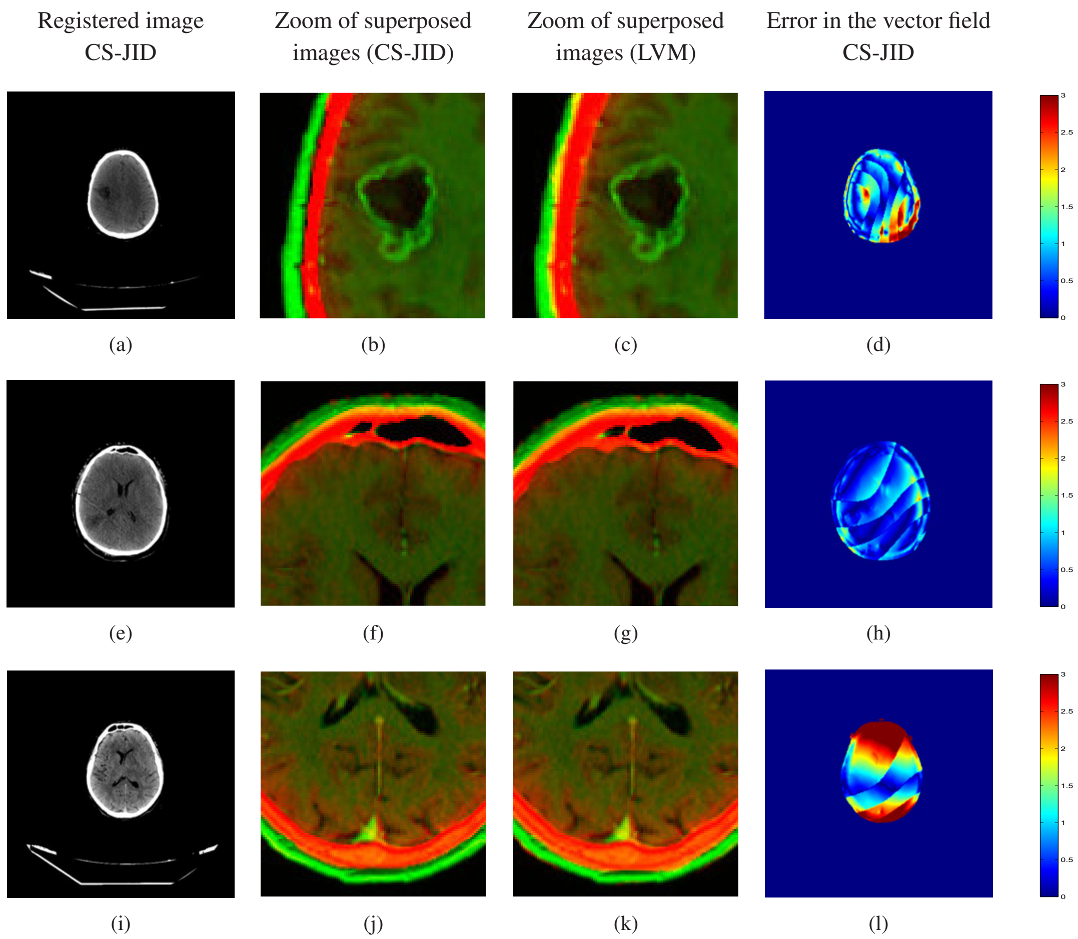

Fig. 2. Registration results with respect to the GTs for CS-JID and LVM. Subfigures (a), (e) and (i) illustrate the source image warped by the proposed method based on CS-JID, for the three GTs. Subfigures (b), (f) and (j) show a zoom of the superposed images in BGR, warped registered source image by the CS-JID method, source image in red channel and target in green channel. Subfigures (c), (g) and (k) present a zoom of the superposed images in BGR, warped source image by LVM method, source image in red channel and target in green channel. Subfigures (d), (h) and (l) ilustrate the error in the estimation of displacements vector field obtained by the proposed method CS-JID.

field. First, the parameters of a geometric transformation are obtained by a PF optimization, which provides an initial estimation in our problem. Next, an OF algorithm is employed to iteratively approximate the remaining deformation vector field. After analyzing the experiments and results shown in this work, we can appreciate that the proposed method has good performance for multimodal NRR. Furthermore, according to the results, the algorithm can be considered as a good alternative for multimodal medical applications. Other important result is the halo reduction in the cerebrospinal fluid of the CT by our method, which better defines the skull and the gray matter edges in the CT image. This property of the new method highlights its medical application compared to the LVM algorithm [17] . In future work, the CS-JID algorithm will be further improved to seek an increase in accuracy performance. One possible research direction is to modify the regularization term in the proposed energy function to an adaptive structure which could be more consistent with the behaviour of the deformations in medical imaging. Also, a more detailed evaluation is necessary of the algorithm by using error indicators for medical images registration, and a comparison with other methods in the literature, for example schemes based on demons [25]. Finally, an implementation for volume registration will be also explored as future work.

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